

Barbachyn *et al.* is described in the Office Action as disclosing “antimicrobial oxazolidinone derivatives, such as linezolid, wherein said compounds are formulated into compositions for treating patients suffering microbial infections,” and administration of such compounds “orally, parenterally (by injection, intravenous injection or infusion) or topically ...” (Office Action, p. 3). The Office Action goes on to note, however, that Barbachyn *et al.* does “not disclose adding a cyclodextrin compound to the composition and methods.”

Bartoli *et al.* is cited as disclosing “orally active antifungals wherein said antifungals are formulated into injectable compositions containing an aqueous carrier and cyclodextrins, e.g. Hydroxypropyl-beta-cyclodextrin, as solubilizing agents.” (Office Action, pp. 3 and 4). The Office Action goes on to state that:

“It would have been obvious to one of ordinary skill in the art to modify the methods and composition of Barbachyn *et al.* to include the cyclodextrins taught by Bartoli *et al.* because Bartoli *et al.* disclose that the cyclodextrins enhance the solubility of the antifungal agents.” (Office Action, p. 4)

Applicant respectfully disagrees with this last statement, and submits that the subject matter of claims 1-30 of the present application would not have been obvious to one of ordinary skill in the art over Barbachyn *et al.* in view of Bartoli *et al.*, for the following reasons and for reasons set forth in the accompanying Declaration by Dr. Michael R. Barbachyn, Under 37 CFR §1.132. Note, incidentally, that Dr. Barbachyn is also one of the inventors of the subject matter of the Barbachyn *et al.* patent.

In order to establish a *prima facie* case of Obviousness, the Manual of Patent Examining Procedure (8<sup>th</sup> edition, August 2001; hereinafter, “MPEP”) states that the following three basic criteria must be met:

“First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.” MPEP, section 2143.

Applicant submits that neither the references themselves nor knowledge generally available to one of ordinary skill in the art would have suggested or motivated one to combine the reference teachings in the way suggested in the Office Action. In paragraph 7 of his Declaration, Dr. Barbachyn describes the structure of cyclodextrins, noting that cyclodextrins have a doughnut shape, with a “hydrophobic cavity that can incorporate a variety of guest

molecules of suitable size and shape, resulting in increased solubility of many different poorly soluble, lipophilic drugs in the presence of cyclodextrins.” Dr. Barbachyn goes on to state that hydrophobic interaction is generally considered to be “the most important factor responsible for the incorporation of guest molecules into the hydrophobic interior of a cyclodextrin cavity.” (Declaration, paragraph 7). Dr. Barbachyn also observes that:

“The azole antifungal agents described as being solubilized by cyclodextrins in Bartoli *et al.* are examples of the very type of poorly soluble lipophilic drugs of a suitable size and shape to fit into the hydrophobic interior of a cyclodextrin cavity that one would expect to be solubilized by cyclodextrins.” (*Id.*)

In the next six paragraphs of the Declaration, Dr. Barbachyn discusses the many differences, in size, structure, lipophilicity, pK<sub>a</sub>, and functionality between the azole antifungal agents solubilized with cyclodextrin compounds as disclosed by Bartoli *et al.*, and the oxazolidinone compounds disclosed by Barbachyn *et al.* Two compounds from Bartoli *et al.* and one compound from Barbachyn *et al.* (linezolid) were used, by way of illustration, in the discussion. However, in paragraph 13, Dr. Barbachyn notes that the same general [physical and functional] characteristics discussed with respect to each compound would be expected to apply to the entire class of compounds of which each compound is a member (i.e., oxazolidinone or azole antifungal agent). Dr. Barbachyn concludes by stating that:

“[T]he size, molecular weight, hydrophobicity, and basicity of the azole antifungal compounds are too different from those same properties of the oxazolidinones, including linezolid, for one to expect the oxazolidinones to be solubilized in the presence of cyclodextrins merely because the same can be said of the azole antifungal compounds.” (Declaration, paragraph 13).

In view of the above, Applicant respectfully submits that the Office Action has not established a *prima facie* case of obviousness in the present case, because, as demonstrated above and by the Barbachyn Declaration, one of ordinary skill in the art would not have been motivated to combine or modify the teachings of Barbachyn *et al.* and Bartoli *et al.* to include a cyclodextrin in an oxazolidinone composition, both of which are elements of claim 1. The MPEP notes that:

If an independent claim is nonobvious under 35 USC 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). MPEP 2143.02.

For reasons set forth above, therefore, Applicant respectfully requests that the rejection of claims 1-30, under 35 U.S.C. §103(a), over Barbachyn *et al.* in view of Bartroli *et al.* be withdrawn.

### III. SUMMARY

For reasons set forth above, Applicants submit that all the claims pending in the present case (i.e., claims 1-30) are in condition for allowance. Issuance of all the claims is, therefore, requested. The Examiner is invited to contact the undersigned at the telephone number given below, should she wish to discuss any of the above.

Respectfully submitted,



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**MARKED-UP COPY OF AMENDED CLAIMS**

The following is copy of all claims amended herein above, submitted in marked-up form, in accordance with 37 CFR §1.121(c)(1)(ii). Changes are shown, below, by brackets (“[ ]”) for deleted matter and by underlining for added matter.

12. (Amended) The composition of Claim 1 wherein the cyclodextrin compound is selected from the group consisting of  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin,  $\gamma$ -cyclodextrin, alkylcyclodextrins [(*e.g.*, methyl- $\beta$ -cyclodextrin, dimethyl- $\beta$ -cyclodextrin, diethyl- $\beta$ -cyclodextrin)], hydroxyalkylcyclodextrins, carboxyalkylcyclodextrins and sulfoalkylether cyclodextrins.